D-2935 CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of:

Roger Aoki et al	)	
	)	Examiner: N/A
Serial No. PENDING	)	
	)	
Filed: HEREWITH	)	Art Unit: N/A
	)	
For: TREATMENT OF NEUROMUSCULAR DISORDERS AND CONDITIONS WITH DIFFERENT BOTULINUM SEROTYPE	)	

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on April 30, 2001.

Signed: Jean F. Heuler
Name: Jean F. Heuler
Date: April 30, 2001

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Please amend the above-identified application as follows:

In the Specification

Page 1, line 4, please add the following:

Related Application

The present application is a continuation of co-pending application serial no. 08/075,048, filed June 10, 1993, the disclosure of which is incorporated in its entirety herein by reference.

In the Claims

Cancel claims 1 to 10, without prejudice.

Add the following new claims 11-13 as follows:

11. (New) A method of treating a muscular spasm, said method comprises the steps of

(a) administering a therapeutically effective amount of a botulinum toxin type A to a human; and

(b) administering a therapeutically effective amount of a botulinum toxin type E to the human after the human exhibits a substantially reduced response to the administration of botulinum toxin type A.

12. (New) A method of treating a muscular spasm, said method comprises the steps of

(a) administering a therapeutically effective amount of a botulinum toxin type A to a human; and

(b) administering a therapeutically effective amount of a botulinum toxin type E to the human after the human develops neutralizing antibodies to the botulinum toxin type A.

13. (New) A method of treating a muscular spasm, said method comprises the steps of

(a) administering a therapeutically effective amount of a botulinum toxin type A to a human; and

(b) administering a therapeutically effective amount of a botulinum toxin type E to the human before the human

exhibits a substantially reduced response to the administration of botulinum toxin type A and B.

REMARKS

The above-identified application has been carefully reviewed in light of the February 28, 2001, Board's decision on the prior (parent) application serial no. 08/075,048, filed June 10, 1993.

Claims 1 to 10 have been canceled without prejudice.

New Claims 11, 12 and 13 have been added to further clarify the invention. These pending claims are fully supported by the specification. For example, new claim 11 is supported by Example 1 (c) of the specification (page 14); claim 12 is supported by the specification on page 7, lines 15-22; and, claim 13 is supported by the specification on page 6 line 28 to page 7 line 2.

The applicant further submits that the subject matters in pending claims 11, 12 and 13 are novel at the priority filing date (June 10, 1993) of this application. That is, no one has administered botulinum toxin type A followed by an administration of botulinum toxin type E prior to the priority filing date of this application.

Additionally, the applicant submits that the subject matters in claims 11, 12 and 13 are not obvious at the priority filing date of this application.

To establish a prima facie case of obviousness, the Examiner carries the burden of showing that there is a substantial likelihood of success that the combination of the prior art would perform in accordance with the claimed invention. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d, 1788, 1790 (Bd. Pat. App.

& Int. 1986); and *Amgen, Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

There is no single prior art reference or set of references that discloses, teach or even suggest that the administration of botulinum toxin type E will be therapeutically effective after the patient is treated with botulinum toxin type A. To the applicant's knowledge, the prior art references that most closely relates to pending Claims 11, 12 and 13 are Ludlow et al. *The New England Journal of Medicine*, Vol. 326(5), page 349, January 1992; Simpson, *Pharmacological Reviews*, Vol. 33(3), pages 155-158, 1981; and Jankovic and Brin, *The New England Journal of Medicine*, Vol. 324, pages 1186-1194, 1991. However, these references, separately or in combination, do not make obvious the present invention. For example, these references may only teach that botulinum toxin type F may be administered after the botulinum toxin type A ceases to be therapeutically effective. At most, these references would only make it "obvious to try" to administer botulinum toxin type E after type A exhibits a substantially reduced capability to provide a therapeutic effect. However, if the prior art references only make it "obvious to try" without providing for any expectation of success, the references do not make obvious the invention. *Hybritech Inc.* 231 USPQ 81 (Fed. Cir. 1986).

<u>No Likelihood of Success</u>

Applicant submits that no prior art references, individually or in combination, including Ludlow et al., Simpson and Jankovic, provide that there is a likelihood of success that the administration of type E will be therapeutically effective after the administration of

botulinum toxin type A provides a substantially reduced therapeutic effect on a human.

Applicant acknowledges that the various serotype toxins may have some properties that are similar. For example, these toxins may all reduce acetylcholine release.[1] Moreover, applicant acknowledges that each of the serotype toxins may be antigenically distinct.

However, the fact that the various toxin serotypes may have similar properties and are antigenically distinct does not make it obvious that an administration of one type of botulinum toxin will be successful, i.e., therapeutically effective, when administered subsequently to another type of botulinum toxin. Simply put, there is no expectation of success that administration of one particular type of botulinum toxin will be therapeutically effective after the administration of another type of botulinum toxin provides a substantially reduced response in a human. Among the reasons for such lack of expectation of success is the fact that the activities of the antibodies generated from each serotype

[1] Although all serotype toxins reduce the release of acetylcholine, it was well recognized prior to the filing date of the above-identified application that the various botulinum serotypes do have very different properties. For example, serotype toxins inhibit acetylcholine release by affecting different neuro secretory proteins and/or cleaving these proteins at different sites. This is evidenced by, for example, the article by Simpson et al presently cited by the Examiner. Thus, for example, botulinum toxins types A and E both cleave the 25KD synaptosomal associated protein (SNAP-25), but they target different amino acid sequences within this protein. Botulinum neuro toxin types B, D, F and G act on vesicle-associated membrane protein (VAMP) with each serotype cleaving the protein at a different site. Finally, botulinum toxin type C has been shown to cleave both syntaxin and SNAP-25.

Furthermore, not only are the various botulinum toxin serotypes different in their relative activities, but they are also different with regard to their structures. For example, type A is produced in both a 900kD and a 500kD form, types B and C_1 are produced as a 500kD complex only, type D as both a 300kD and 500kD form and types E and F as approximately 300kD complexes only.

toxin is unpredictable, one from the other. That is, it is totally unpredictable whether or not an antibody to one serotype botulinum toxin has cross-over reactivity to block the effectiveness of another serotype toxin administered subsequently.

Because it is highly unpredictable whether the administration of one type of botulinum toxin will work after the administration of another type of botulinum toxin provides a substantially reduced response in a human, there can be no likelihood of success that an administration of any type of botulinum toxin will be therapeutically effective after the administration of type A type of botulinum toxin provides a substantially reduced response in a human. Much less, there would be no expectation of success that botulinum toxin type E will be therapeutically effective after the administration of type A type of botulinum toxin provides a substantially reduced response in a human.

For example, it was well known in the art at the time of filing of the above-identified application that antibodies to serotype botulinum toxin C_1 bind to serotype botulinum toxin D (Tsuzunki et al., *Infection and Immunity* 56(4):898 (1988)); antibodies to serotype toxin type E bind to serotype toxin F (Siegel, *Journal of Clinical Microbiology* 27(8):1906 (1989)); and antibodies to serotype toxin F bind to serotype botulinum toxin D (Ferreira, *Applied and Environmental Microbiology* 56(3):808 (1990)). (A copy of each of these Articles is submitted herewith.) Furthermore, it is also well known that the ability of an antibody to bind to a toxin may be related to the ability of the antibody to block the effectiveness of the toxin. As such, the administration of botulinum toxin type D may not have any therapeutic effect after the administration of type C_1 stops to provide therapeutic effects; the administration of botulinum toxin type F may not have any

therapeutic effect after the administration of type E stops to provide therapeutic effects; and the administration of botulinum toxin type F may not have any therapeutic effect after the administration of type D stops to provide therapeutic effects. Similarly, there is no likelihood that the administration of botulinum toxin type E will be successful in treating spasm after the administration of type A type of botulinum toxin provides a substantially reduced response in a human.

Furthermore, there are other well known factors relating to antibody production that would teach one of ordinary skill away from using serotype toxin E after treatment with serotype toxin A. For example, it was known at the time the above-identified application was filed that botulinum toxins are initially synthesized as inactive single chain proteins. These inactive single chain proteins must be cleaved or "nicked" by proteases before becoming neuro active. The bacterial strains that make serotypes toxins A and G possess endogenous proteases. See, for example, the article by Bonventre *et al* (Journal of Bacteriology, 1960:79:24-32)(enclosed). Consequently these serotypes are recovered from bacterial cultures predominantly in their active form. In contrast, types C_1, D and E are synthesized by non-proteolytic strains and are therefore inactive when recovered from culture. Serotypes B and F are produced by proteolytic and non-proteolytic strains and may be recovered in either the active or inactive forms.

The presence of inactive botulinum toxin molecules in a clinical preparation will contribute to the overall protein load of the preparation. An overall protein load has been linked to increased production of antibodies, which may neutralize the toxins. Accordingly, one of ordinary skill would be led away from using serotype toxin E in clinical

practice because it may cause an increase in antibody production. In other words, it may have been reasonable to consider using serotype toxin F for treating patients who have become unresponsive to botulinum toxin A, for example, on the basis that botulinum toxin F can be produced in an active form by the same bacteria that produce botulinum toxin A. However, there is no motivation for one of ordinary skill to combine the teachings of Simpson, Jankovic et al and/or Ludlow to replace botulinum toxin F with toxin E, in particular since, as stated above, toxin E is produced in an inactive form and therefore may promote a higher level of antibody to block toxin activity.

Therefore, applicant submits that the presently pending claims 11 to 13 are novel. Furthermore these pending claims are unobvious because there is no likelihood of success that the administration of type E will be therapeutically effective after the administration of type A type of botulinum toxin provides a substantially reduced response in a human.

Applicant respectfully requests early and favorable action in the above-identified application. Should any matters remain unresolved, the Examiner is requested to call applicant's attorney at the telephone number given below.

Respectfully submitted,

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